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EXAMINER

GUNTER, DAVID R

ART UNIT	PAPER NUMBER
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1634

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8

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

09/979,545

Applicant(s)

HWANG ET AL.

Examiner

David R. Gunter

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☐ Responsive to communication(s) filed on ____.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-18 is/are pending in the application.
- 4a) Of the above claim(s) 18 is/are withdrawn from consideration.
- 5) ☐ Claim(s) ____ is/are allowed.
- 6) ☒ Claim(s) 1-17 is/are rejected.
- 7) ☐ Claim(s) ____ is/are objected to.
- 8) ☒ Claim(s) 1-17 are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on ____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
- Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on ____ is: a) ☐ approved b) ☐ disapproved by the Examiner.
- If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

- 13) ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☒ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. ____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.
- 14) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).
- a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

- 1) ☐ Notice of References Cited (PTO-892) 4) ☐ Interview Summary (PTO-413) Paper No(s). ____
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948) 5) ☐ Notice of Informal Patent Application (PTO-152)
- 3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) ____ 6) ☐ Other: ____

DETAILED ACTION

Restriction Requirement

Restriction to one of the following inventions is required under 35 U.S.C. 121:

- I. Claims 1-17, drawn to a method for identifying a DNA mutation, classified in class 436, subclass 94.
- II. Claim 18, drawn to a kit, classified in 435, subclass 288.3

Inventions I and II are related as product and process of use. The inventions can be shown to be distinct if either or both of the following can be shown: (1) the process for using the product as claimed can be practiced with another materially different product or (2) the product as claimed can be used in a materially different process of using that product (MPEP § 806.05(h)). In the instant case, the kit recited in claim 18 can be used in a plurality of processes materially different from the method of invention I. The amine groups present in the microwell can be chemically linked to a number of distinct classes of molecules, including polypeptides, and the solutions present in the kit can be used to detect binding of a plurality of substrates to the linked molecule. For example, the kit as recited could be used to identify DNA molecules which bind to immobilized polypeptides.

Because these inventions are distinct for the reasons given above and have acquired a separate status in the art because of their recognized divergent subject matter, restriction for examination purposes as indicated is proper.

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1. During a telephone conversation with Che Chereskin on 11/07/02 a provisional election was made with traverse to prosecute the invention of group I, claim 1-17. Affirmation of this election must be made by applicant in replying to this Office action. Claim 18 is withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention.

2. Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a request under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

Specification

3. The use of the trademarks Tween-20TM and Triton X-100TM have been noted in this application. It should be capitalized wherever it appears and be accompanied by the generic terminology.

Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner which might adversely affect their validity as trademarks.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

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The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

4. Claims 1-17 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

a. Regarding claims 1-17, the claims are drawn to a method of identifying a DNA mutation, however the method steps only recite immobilization of a probe to a microwell, hybridizing amplified DNA to the probe, and detecting hybridization. It is not clear how these method steps accomplish the recited objective of identifying a DNA mutation. The claims should be amended either to add the method steps necessary to accomplish the identification of a DNA mutant or to clarify how detection of hybridization accomplishes the recited objective of the method.

b. Claims 1-17 are indefinite for the recitation in claim 1 of “corresponding to the DNA sequence to be identified.” The term “corresponding” is a non-specific relational term, therefore the relationship between the normal sequence and the DNA sequence to be identified is undefined. It is suggested that the claim be amended to define this relationship.

c. Regarding claim 1(iii), the phrase “the amine group of the microwell” lacks antecedent basis in the claims. There is no prior recitation of the presence of amine groups on the surface of the microwells, nor is there recitation of the placement of such a group onto the surface of the microwells.

d. Regarding claim 4, the phrase “ice cold” is indefinite. “Ice cold” can refer to object at or near the temperature of 0° Celsius or to objects at or near the temperature of

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dry ice. The claims should be amended to recite a specific temperature or range of temperatures.

e. Claims 5, 7-9, 11, and 13 contain the trademark/trade names Tween-20TM and Triton X-100TM. Where a trademark or trade name is used in a claim as a limitation to identify or describe a particular material or product, the claim does not comply with the requirements of 35 U.S.C. 112, second paragraph. See *Ex parte Simpson*, 218 USPQ 1020 (Bd. App. 1982). The claim scope is uncertain since the trademark or trade name cannot be used properly to identify any particular material or product. A trademark or trade name is used to identify a source of goods, and not the goods themselves. Thus, a trademark or trade name does not identify or describe the goods associated with the trademark or trade name. In the present case, the trademark/trade name is used to identify/describe detergents contained in various solutions used in the method and, accordingly, the identification/description is indefinite.

f. Regarding claims 5, 7, 8, 9, 11, and 13, the use of the “/” symbol between reagents in the recitation of the buffer compositions is unclear. If in claim 5, for example “0.4M NaOH/0.25% Tween 20” is meant to recite a solution comprising 0.4M NaOH and 0.25% Tween 20TM, the claims should be amended to make this recitation clear. In addition, recitations of concentrations of reagents by a percentage should include the basis on which the percentage is calculated (weight to weight, weight to volume, etc.)

g. Regarding claim 6:

i) The phrase “the probe of microwell” is indefinite because the meaning is not clear. The claim should be amended to indicate that the probe recited in claim

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6 is the probe affixed to the amine group present on the surface of the microwell as described in claim 1 (iii).

ii) The phrase “residual DNA fragments” is indefinite because the meaning is not clear. The claim should be amended to indicate that the residual DNA fragments are the unbound biotin-labeled PCR products from claim 1, step (i).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

5. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

6. Claims 1-3, 5, and 16 are rejected under 35 U.S.C. 103(a) as being unpatentable over Saiki, et al., Proc Natl Acad Sci USA 86:6230-6234, 1989 (hereinafter referred to as “Saiki”) in view of Zammateo, et al., Analytical Biochemistry 236:85-94, 1996 (hereinafter referred to as

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“Zammatteo”). Claim 1 recites a method for identifying DNA mutations using microwells which comprises the steps of (i) preparing amplified biotinylated DNA fragments of a portion of nucleotide sequence to be identified by PCR using a biotin-bound primer; (ii) preparing a probe comprising normal sequence corresponding to the DNA sequence to be identified; (iii) affixing the probe prepared in step (ii) to the amine group of the microwell; (iv) adding biotinylated DNA fragments prepared in step (i) to the probe-affixed microwell; (v) adding a streptavidin-linked degradation enzyme to the microwell in order to bind the degradation enzyme to the biotin moiety of the probe-captured sample DNA fragment; and (vi) adding a substrate to be reacted with the degradation enzyme and detecting the color or absorbance change caused by degradation of the substrate.

Saiki teaches a method for identifying DNA mutations that is essentially identical to that of the current application. In the method of Saiki, biotinylated DNA fragments were prepared by amplifying a portion of a nucleotide sequence to be identified using PCR with biotinylated amplification primers (page 6231, left column, third paragraph). Probes comprising the normal sequence were prepared (page 6230, right column, last paragraph; also page 6231, right column, last paragraph) and attached to a solid support (page 6231, left column, second paragraph). The biotinylated DNA fragments were added to the bound probes, and a streptavidin-linked degradation enzyme was added and allowed to bind to the biotin moiety of the probe-captured sample DNA complex. A substrate was reacted with the degradation enzyme, and the change in color caused by the degradation of the substrate was detected (page 6231, left column, fourth paragraph).

Saiki teaches that the DNA probe is affixed to a solid support, but does not specifically teach that the probe is linked to a microwell by attachment of the probe to an amine group on the surface of the microwell. Zammattéo, however, teaches a method of identifying DNA mutations similar to that of the instant application, and teaches that the probes are linked to a microwell by covalent bonding to an amine group on the surface of the well (page 87, right column, second paragraph). Zammattéo teaches that “[c]apture probes bound to aminated microwells at only the 5’ end represents ideal configuration for hybridization with its complementary strand” because it provides a permanent linkage of the probe to the substrate without interfering with the ability of the probe to hybridize to a complementary DNA strand (page 90, right column, last paragraph; page 87, right column, second paragraph). Furthermore, Zammattéo teaches that the “amination of polystyrene is easy to carry out and requires only materials available in any laborator[y]” (page 94, left column, first paragraph). It would have been obvious to one of ordinary skill in the art at the time the application was filed to modify the technique of Saiki to include attachment of DNA probes to a microwell by covalent linkage to an amine group for three reasons: first, because it would provide a permanent attachment to the substrate without interfering with hybridization of the probe to its complement; second, the technique is easily carried out with materials that are readily available; and third, microwells were well known to those of ordinary skill in the art for the convenience with which they could be used for binding assays such as ELISA as taught by Zammattéo (page 90, right column, last paragraph; page 87, right column, second paragraph).

- a. Regarding Claim 2, Saiki teaches the embodiment in which the probes are more than ten nucleotides in length (page 6232, table 1), and Zammattéo teaches the

embodiment in which the oligonucleotides comprise a phosphate moiety on the 5' end (page 87, right column, second paragraph).

b. Regarding Claim 3, Zammatteo teaches the embodiment in which single stranded DNA probes are added to the microwell, catalysts are added in order to bind the phosphate moiety of the probe to the amine group of the microwell, and the microwell is washed (page 87, right column, second paragraph).

c. Regarding Claim 5, Zammatteo teaches the embodiment in which the microwells are washed with 0.4N NaOH, 0.25% Tween 20TM (page 87, right column, second paragraph).

d. Regarding claim 16, Saiki teaches the embodiment in which the color change is detected visually (page 6231, left column, fourth paragraph; also page 6233, figure)

7. Claim 4 is rejected under 35 U.S.C. 103(a) as being unpatentable over Saiki in view of Zammatteo in further view of Rasmussen, et al., Analytical Biochemistry 198:138-142, 1991 (hereinafter referred to as "Rasmussen"). Claim 3 is rejected as being unpatentable over Saiki in view of Zammatteo as described above in paragraph 9. Claim 4 recites the additional limitations to claim 3 that the catalysts to be used to bind the phosphate moiety of the single-stranded probe to the amine group of the microwell are ice-cold solutions of 10 mM 1-methylimidazole, pH 7.0, and 1-ethyl-3-(3-dimethylaminopropyl)-carbodiimide (EDC), pH 7.0.

Zammatteo teaches the embodiment in which the catalysts are ice-cold solutions of 10mM 1-methylimidazole, pH 7.5 and 0.2M EDC (Zammatteo page 87, right column, second paragraph; further described in detail in Rasmussen, page 139, left column, second paragraph).

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Neither Zammatteo nor Rasmussen teach the pH of the 1-methylimidazole solution. It is noted that *In re Aller*, 220 F.2d 454,456, 105 USPQ 233,235 states where the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum by routine experimentation. It would have been obvious to one of ordinary skill in the art at the time the application was filed to optimize the method of Saiki as modified by Zammatteo and Rasmussen by altering the pH of the solution in order to maximize binding of the phosphate moiety of the single-stranded probe to the amine group of the microwell.

8. Claims 6 and 10 are rejected under 35 U.S.C. 103(a) as being unpatentable over Saiki in view of Zammatteo in further view of Zammatteo, et al., *Journal of Virological Methods* 55:185-197, 1995 (hereinafter referred to as "Zammatteo 95")

a. Regarding claim 6, the method of claim 1 is rejected as being unpatentable over Saiki in view of Zammatteo as described above in item number 5. Claim 6 recites the additional limitations to claim 1 that step (iv) comprises binding the single-stranded DNA fragments obtained in step (i) to the probe affixed to the microwell, removing the residual DNA fragments, and washing the microwell.

Zammatteo teaches a method in which single stranded DNA fragments obtained by PCR using a biotin-bound primer are bound to the probe affixed to the microwell, and in which the residual DNA fragments are removed and the microwell is washed (Zammatteo page 87, right column, third paragraph; described in detail in Zammatteo 95, page 188, third paragraph through page 190, first paragraph). It would have been obvious to one of ordinary skill in the art at the time the application was filed to modify

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the method of Saiki as modified by Zammatteo to include the binding and washing steps of Zammatteo 95 in order to remove DNA fragments which were not affixed to the microwell. One of ordinary skill in the art would have been motivated to include these binding and washing steps because any residual, unaffixed DNA fragments would compete with affixed fragments for binding to the streptavidin-bound degradation enzyme, resulting in a loss of signal intensity.

b. Regarding Claim 10, Zammatteo 95 teaches the embodiment in which the microwell is washed, a streptavidin-linked degradation enzyme is introduced and allowed to bind to biotin, the residual reaction mixture is removed, and the microwell is washed again (Zammatteo 95, page 188, third paragraph).

9. Claims 7 and 8 are rejected under 35 U.S.C. 103(a) as being unpatentable over Saiki, in view of Zammatteo, in further view of Zammatteo 95, in further view of Felder and Kris, USPN 6,232,066, filed July 2, 1998, issued May 15, 2001 (hereinafter referred to as "Felder"). Claim 6 is rejected as being unpatentable over Saiki in view of Zammatteo in further view of Zammatteo 95 as described above in item 7(a). Claim 7 recites the additional limitations to claim 6 that the microwells are pre-treated with a solution containing dH₂O, 20x SSPE / 0.0167% Triton X-100TM and 10 mg/ml salmon sperm DNA at 50°C for 20 minutes before adding the single-stranded DNA fragments obtained in step (i) to the microwell. Claim 8 recites the additional limitations to claim 6 that the binding of the DNA fragments obtained in step (i) to the probe occurs in a solution containing dH₂O, 20x SSPE, 0.0167% Triton X-100TM, and 10 mg/ml salmon sperm DNA.

Neither Saiki nor Zammetteo teach the specific buffer recited in claim 7. However, the use of hybridization buffers containing SSPE, Triton X-100TM, and salmon sperm DNA were well known to those of ordinary skill in the art at the time the application was filed (see, for example Felder, column 30, line 39, and column 12, lines 13-15). It would have been obvious to one of ordinary skill in the art at the time the application was filed to modify the method of Saiki to include the buffer of Felder. One of ordinary skill would have been motivated to include the buffer of Felder due to the presence of salmon sperm DNA, an agent known to block non-specific binding of DNA (Felder, column 12, lines 13-15).

Although the buffer described by Felder is used for the hybridization of oligonucleotides and not the pre-treatment of bound oligonucleotides prior to hybridization, it was well known to those of ordinary skill in the art at the time the application was filed that hybridization buffer could be used to pre-treat bound oligonucleotides prior to hybridization. Sakai, for example, first adds hybridization buffer to the bound oligonucleotides, and then adds the biotin labeled single-stranded DNA fragments (page 6231, left column, fourth paragraph).

Felder does not teach the specific concentrations of SSPE, Triton X-100TM, or salmon sperm used in the instant application. Neither Saiki nor Felder teach that the pre-treatment takes place at 50°C for 20 minutes. However, it would have been obvious to one of ordinary skill in the art at the time the application was filed to optimize the method of Saiki and the buffer of Felder in order to minimize non-specific binding of the single-stranded probe.

- a. Regarding Claim 8, Felder teaches the embodiment in which the binding of DNA to a probe occurs in a solution containing dH₂O, SSPE, Triton X-100TM, and salmon sperm DNA. Felder does not teach the specific concentrations of SSPE, Triton X-100TM,

or salmon sperm used in the instant application. However, it would have been obvious to one of ordinary skill in the art at the time the application was filed to optimize the method of Saiki and the buffer of Felder in order to maximize specific binding of the single-stranded probe.

10. Claim 9 is rejected under 35 U.S.C. 103(a) as being unpatentable over Saiki in view of Zammatteo in further view of Zammatteo 95 in further view of Villeponteau, et al., USPN 5,776,679, filed June 7, 1995, issued July 7, 1998 (hereinafter referred to as "Villeponteau"). Claim 6 is rejected as being unpatentable over Saiki in view of Zammatteo in further view of Zammatteo 95 as described above in item 7. Claim 9 recites the additional limitations to claim 6 that the washing is performed by employing 0.5x SSC and 0.1% Tween-20TM.

Saiki teaches the embodiment in which the single-stranded DNA probes affixed to the solid support are washed with 2x SSPE and 0.1% SDS. Saiki does not specifically teach the use of SSC or Tween-20TM. However, the use of buffers containing SSC and Tween-20TM was well known to those of ordinary skill in the art at the time the application was filed (see for example Villeponteau, column 42, line 4). It would have been obvious to one of ordinary skill in the art to substitute the buffer of Villeponteau for the buffer of Saiki. One of ordinary skill in the art would have been motivated to substitute the buffer due to the constraints of experimental design, including possible interactions of SDS or the phosphate or EDTA present in SSPE with other reagents used in the detection method. Villeponteau does not teach the specific concentrations of SSC and Tween-20TM recited in the instant application. However, it would have been obvious to

one of ordinary skill in the art at the time the application was filed to optimize the buffer of Villeponteau in order to minimize non-specific binding of the single-stranded probe.

11. Claim 11 and 13 are rejected under 35 U.S.C. 103(a) as being unpatentable over Saiki, in view of Zammateo, in further view of Zammateo 95, in further view of Bogdanov, USPN 6,245,507, filed August 18, 1998, issued June 12, 2001 (hereinafter referred to as "Bogdanov"). Claim 10 is rejected under 35 U.S.C. 103(a) as being unpatentable over Saiki in view of Zammateo in further view of Zammateo 95 as described in item 7(b) above. Claim 11 recites the additional limitations to claim 10 that the first washing is performed by employing a buffer solution of 100 mM Tris-HCl, pH 7.5 containing 150 mM NaCl and 0.1% Tween-20TM. Claim 13 recites the additional limitation to claim 10 that the second washing is performed by employing a buffer solution of 100 mM Tris-HCl, pH 7.5 containing 150 mM NaCl and 0.1% Tween-20TM at 60°C for 10 minutes.

Saiki does not teach this specific wash buffer, but instead teaches a wash buffer comprising 2x SSPE and 0.1% SDS (page 6231, left column, fourth paragraph). However, the use of wash buffers containing Tris-HCl, NaCl, and Tween-20TM were well known to those of ordinary skill in the art as taught by Bogdanov, column 22, lines 39-41. It would have been obvious to one of ordinary skill in the art to substitute the buffer of Bogdanov for the buffer of Saiki. One of ordinary skill in the art would have been motivated to substitute the buffer due to the constraints of experimental design, including possible interactions of SDS or the phosphate or EDTA present in SSPE with other reagents used in the detection method. Bogdanov does not teach the specific concentrations of SSC and Tween-20TM recited in the instant application.

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However, it would have been obvious to one of ordinary skill in the art at the time the application was filed to optimize the buffer of Bogdanov in order to minimize non-specific binding of the single-stranded probe.

a. Regarding claim 13, Saiki does not teach this specific wash buffer, but instead teaches a wash buffer comprising 2x SSPE and 0.1% SDS (page 6231, left column, fourth paragraph). However, the use of wash buffers containing Tris-HCl, NaCl, and Tween-20TM were well known to those of ordinary skill in the art as taught by Bogdanov, column 22, lines 39-41. It would have been obvious to one of ordinary skill in the art to substitute the buffer of Bogdanov for the buffer of Saiki. One of ordinary skill in the art would have been motivated to substitute the buffer due to the constraints of experimental design, including possible interactions of SDS or the phosphate or EDTA present in SSPE with other reagents used in the detection method. Bogdanov does not teach the specific concentrations of SSC and Tween-20TM recited in the instant application. However, it would have been obvious to one of ordinary skill in the art at the time the application was filed to optimize the buffer of Bogdanov in order to minimize non-specific binding of the single-stranded probe.

Saiki teaches that the wash steps are carried out at 55°C for 10 minutes (page 6231, left column, fourth paragraph), not at 60°C for 10 minutes as recited in claim 13. However, it would have been obvious to one of ordinary skill in the art at the time the application was filed to optimize the wash conditions by manipulating the temperature in order to minimize non-specific binding of the single-stranded probe.

12. Claim 12 is rejected under 35 U.S.C. 103(a) as being unpatentable over Saiki in view of Zammatteo in further view of Zammatteo 95 in further view of Zreiqat, et al., Molecular Biotechnology, 10:107-113, 1998 (hereinafter referred to as "Zreiqat") in further view of Kit and Kit, USPN 4,711,850, filed January 28, 1986, issued December 8, 1987 (hereinafter referred to as "Kit"). Claim 10 is rejected as being unpatentable over Saiki in view of Zammatteo in further view of Zammatteo 95 as described in item 7(b) above. Claim 12 recites the additional limitations to claim 10 that the streptavidin-linked degradation enzyme is streptavidin-alkaline phosphatase dissolved in a buffer solution of 100 mM Tris-HCl (pH 7.5) containing 150 mM NaCl.

Saiki teaches that the streptavidin-linked degradation enzyme is horseradish peroxidase, not alkaline phosphatase. However, Zreiqat teaches the use of streptavidin-linked alkaline phosphatase to bind to biotin-labeled nucleic acids in order to detect nucleic acids in a microwell (page 107, abstract). It would have been obvious to one of ordinary skill in the art at the time the application was filed to modify the method of Saiki by substituting the streptavidin-linked alkaline phosphatase of Zreiqat for streptavidin-linked horseradish peroxidase. One of ordinary skill in the art would have been motivated to make this substitution by the availability of reagents, or the constraints of experimental design.

Niether Saiki nor Zreiqat specifically teaches the use of a buffer solution of 100mM Tris-HCl (pH 7.5) containing 150 mM NaCl. However, the use of such a buffer for alkaline phosphatase assays was well known to those of ordinary skill in the art as taught by Kit, column 31, lines 9-11. It would have been obvious to one of ordinary skill in the art at the time the application was filed to modify the method of Saiki to include the buffer of Kit because of the

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buffer's known compatibility with alkaline phosphatase assays. Kit does not teach the exact concentrations of Tris-HCl and NaCl recited in the instant application, however it would have been obvious to one of ordinary skill in the art at the time the application was filed to optimize the concentration of Tris-HCl and NaCl in order to maximize the activity of alkaline phosphatase.

13. Claim 14 is rejected under 35 U.S.C. 103(a) as being unpatentable over Saiki in view of Zammattéo in further view of Zammattéo 95 in further view of Stebbins, et al. Analytical Biochemistry 248:246-250, 1997 (hereinafter referred to as "Stebbins"). Claim 1 is rejected as being unpatentable over Saiki in view of Zammattéo in further view of Zammattéo 95 as described above in item 5. Claim 14 recites the additional limitation to claim 1 that the substrate to be reacted with the streptavidin-linked degradation enzyme is a synthetic peptide showing color or absorbance change during the degradation.

Saiki does not teach the use of a synthetic peptide as a substrate for the streptavidin-linked degradation enzyme. However, the use of such synthetic peptides was well known to those of ordinary skill in the art at the time the application was filed. Stebbins, for example, teaches a synthetic peptide that shows a change in color and absorbance after degradation by a degradation enzyme (Stebbins, page 246, abstract). It would have been obvious to one of ordinary skill in the art at the time the application was filed to modify the method of Saiki to incorporate a synthetic peptide that undergoes a color change in response to a degradation enzyme in order to allow a rapid and quantitative measure of the amount of enzyme present in the microwell.

14. Claim 15 is rejected under 35 U.S.C. 103(a) as being unpatentable over Saiki in view of Zammatteo in further view of Zammatteo 95 in further view of Stebbins in further view of Zreiqat. Claim 14 is rejected as being unpatentable over Saiki in view of Zammatteo in further view of Zammatteo 95 view of Stebbins as described above in item 11. Claim 15 recites the additional limitation to claim 14 that the substrate is pNPP (p-nitrophenyl phosphate) provided that the streptavidin-linked degradation enzyme employed is streptavidin-alkaline phosphatase.

Saiki does not teach the use of a pNPP as a substrate for the streptavidin-linked degradation enzyme. However, the use pNPP as a substrate for alkaline phosphatase, and the use of alkaline phosphatase as a reporter for nucleic acid hybridization was well known to those of ordinary skill in the art at the time the application was filed. Zreiqat, for example, teaches a the use of alkaline phosphatase and pNPP in an in situ hybridization technique for the detection of mRNA. (Zreiqat, page 107, abstract). It would have been obvious to one of ordinary skill in the art at the time the application was filed to modify the method of Saiki to incorporate a alkaline phosphatase and pNPP in order to allow a rapid and quantitative measure of the amount of enzyme present in the microwell.

15. Claim 17 is rejected under 35 U.S.C. 103(a) as being unpatentable over Saiki, in view of Zammatteo, in further view of Rueger, USPN 5,610,021, filed Mar 4, 1994, issued March 11, 1997 (hereinafter referred to as "Rueger"). Claim 1 is rejected under 35 U.S.C. 103(a) as being unpatentable over Saiki, in view of Zammatteo as described above in item 5. Claim 17 recites the additional limitation to claim 1 that the absorbance is measured by employing an ELISA

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reader. Zammatteo 95 does not teach the use of an ELISA reader, but does teach the use of a luminometer. An ELISA reader and a luminometer both represent mechanical means of measuring the degree of change in the light absorbed by or produced by a sample. It would have been obvious to one of ordinary skill in the art to modify the method of Zammatteo 95 to include an ELISA reader because of the known ability of the ELISA reader to measure multiple samples simultaneously, greatly improving the speed and simplicity of the assay procedure (Rueger, column 16, lines 9-47).


Any inquiry concerning this communication or earlier communications from the examiner should be directed to David R. Gunter whose telephone number is (703) 308-1701. The examiner can normally be reached on 9:00 - 5:00 M - F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Jones can be reached on (703) 308-1152. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 746-9212 for regular communications and (703) 308-8724 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0198.



David R. Gunter, DVM, PhD
November 19, 2002



B. J. FOLTMAN
PATENT EXAMINER